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(54) Title: INHIBITION OF HAIR GROWTH

(57) Abstract

Mammalian hair growth is reduced by applying to the skin a composition including an inhibitor of cyclooxygenase.

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INHIBITION OF HAIR GROWTH

The invention relates to the inhibition of hair growth.

Arachidonic acid is released from membrane lipids in response to injury or other irritation. The enzyme cyclooxygenase converts arachidonic acid into cyclic endoperoxides commonly known as PGG_2 and PGH_2. The endoperoxides subsequently are converted into prostoglandins, which are the primary mediators of inflammation in the body.

It has now been found that mammalian (including human) hair growth can be inhibited by applying to the skin a composition including an inhibitor of cyclooxygenase in an amount effective to reduce hair growth in the applied area.

The preferred inhibitors are commonly known as non-steroidal anti-inflammatory drugs (NSAIDs). These drugs include compounds from a variety of chemical classes.

One preferred class of NSAIDs are propionic acids, which include α-methyl-4-[2-methylpropyl]benzeneacetic acid (ibuprofen), 6-methoxy-α-methyl-2-naphthaleneacetic acid (naproxen), 2-[3-phenoxyphenyl]propionic acid (fenoprofen), 2-[3-benzoylphenyl]propionic acid

(ketoprofen), gamma-oxo-[1,1'-biphenyl]-4-butanoic acid (fenoprofen), and 6-chloro-α-methylcarbazole-2-acetic acid (carprofen).

Another preferred class of NSAIDs are indoleacetic acids, which include 1-[p-chlorobenzoyl]-5-methoxy-2-methylindole-3-acetic acid (indomethacin), 5-fluoro-2-methyl-1-[(4-(methylsulfinyl)phenyl) methylene)-1H-indene-3-acetic acid (sulindac), 1-methyl-5-[p-toluoyl]pyrrole-2-acetic acid (tolmetin), 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid (diclofenac).

A third preferred class of NSAIDs are salicylates, which include 2-acetoxybenzoic acid (acetylsalicylic acid) and 5-[2,4-difluorophenyl]salicylic acid (diflunisal).

A fourth preferred class of NSAIDs are anthranilic acids, which include 2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid (meclofenamic acid) and 2-[(2,3-dimethylphenyl) amino]benzoic acid (mefenamic acid).

A fifth preferred class of NSAIDs are enolic acids, such as 4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide (tenoxicam).

Other NSAIDs like 4-[6-methoxy-2-naphthyl]-2-butanone (nabumetone) also can be used.

The composition preferably includes a non-toxic dermatologically acceptable vehicle or carrier which is adapted to be spread on the skin. Examples of suitable vehicles are acetone, alcohols, or a cream, lotion, or gel which can effectively deliver the active compound. In addition, a penetration enhancer may be added to the vehicle to further enhance the effectiveness of the formulation.

The concentration of the inhibitor in the composition may be varied over a wide range up to a saturated solution, preferably from 1 to 30% by weight or even more; the reduction of hair growth increases as the amount of inhibitor applied increases per unit area of skin.

The maximum amount effectively applied is limited only by the rate at which the inhibitor penetrates the skin. Generally, the effective amounts range from 100 to 3000 micrograms or more per square centimeter of skin.

The composition should be applied to the area of the body where it is desired to inhibit hair growth. Typically, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and chin. The composition can also be applied to the legs, arms, torso or armpit. The composition is particularly suitable for the treatment of hirsatism. In humans, the composition should be applied once or twice a day, or even more frequently, for at least three months to achieve a perceived reduction in hair growth.

Reduction of hair growth is demonstrated when the frequency of hair removal is reduced, or the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced. Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to

androgens in the hamster.

To evaluate the effectiveness of a particular inhibitor in reducing hair growth, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex). To one organ of each animal 10 μl. of vehicle alone once a day is applied, while to the other organ of each animal an equal amount of vehicle containing the inhibitor is applied. After thirteen applications (one application per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The preferred cyclooxygenase inhibitors were tested according to the above procedure. The results are presented in Table 1; the vehicles used to deliver the inhibitors are reported in Table 2.

TABLE 1

Hair Mass

Compound	Dose	Vehicle	pH	Treated (mg)	Control (mg)	Percent Inhibition
Propionic acids						
Ibuprofen	20%	B	5.0	1.160 ± .16	1.704 ± .15	30.33 ± 7.74
Naproxen	20%	A	8.5	0.771 ± .11	2.108 ± .15	62.52 ± 5.40
Fenoprofen	20%	D	6.0	0.373 ± .10	1.276 ± .11	70.58 ± 7.04
Ketoprofen	20%	B	4.5	0.895 ± .20	1.293 ± .26	29.70 ± 5.10
Carprofen	20%	C	6.0	0.776 ± .11	1.274 ± .19	29.69 ±11.06
Indoleacetic acids						
Indomethacin	20%	A	8.0	0.307 ± .08	1.844 ± .28	83.78 ± 3.66
Sulindac	20%	A	9.0	0.517 ± .09	2.539 ± .27	79.90 ± 3.27
Tolmetin	20%	A	8.5	1.459 ± .16	2.344 ± .24	37.85 ± 3.35
Diclofenac	20%	B	8.0	0.648 ± .10	1.769 ± .19	63.40 ± 5.21

TABLE 1 (Continued)

Hair Mass

Compound	Dose	Vehicle	pH	Treated (mg)	Control (mg)	Percent Inhibition
Salicylates						
Acetyl-salicylic acid	20%	B	5.0	2.126 ± .33	3.194 ± .21	34.89 ± 7.91
Diflunisal	20%	D	5.0	0.985 ± .10	1.779 ± .18	38.32 ±10.73
Anthranilic acids						
Meclofenamic acid	20%	A	8.5	0.719 ± .14	2.144 ± .18	67.77 ± 4.79
Mefenamic acid	10%	A	8.8	0.518 ± .13	1.520 ± .11	67.18 ± 6.03
Enolic acids						
Tenoxican	15%	B	8.0	0.326 ± .08	2.116 ±0.24	85.38 ± 2.91
Other						
Nabumetone	15%	E	6.0	1.267 ± .23	1.684 ± .21	23.23 ±10.41

TABLE 2

Vehicles Used in Hair Mass Assays

Vehicle A:	68% Purified water, 16% ethanol (200 proof), 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol, 2% propylene carbonate.
Vehicle B:	80% Ethanol (190 proof), 17.5% purified water, 2% propylene glycol dipelargonate, 0.5% propylene glycol.
Vehicle C:	30% Dipropylene glycol, 25% acetone, 15% ethanol (200 proof), 10% benzyl alcohol, 10% dimethyl sulfoxide (DMSO), 10% propylene glycol.
Vehicle D:	35% Dipropylene glycol, 30% ethanol (200 proof), 20% acetone, 10% propylene glycol, 5% benzyl alcohol.
Vehicle E:	35% Dipropylene glycol, 30% ethanol (200 proof), 25% acetone, 10% benzyl alcohol.
Vehicle F:	35% Dipropylene glycol, 35% ethanol (200 proof), 15% acetone, 10% DMSO, 5% benzyl alcohol.

A preferred inhibitor, indomethacin, was tested for inhibition of hair growth in various formulations. The results are presented in Table 3.

TABLE 3

Hair Growth Inhibition by Indomethacin in Various Formulations

Formulation	pH	Hair Mass		Percent Inhibition
		Treated (mg)	Control (mg)	
5% in Vehicle A	7.5	1.248 ± .20	2.173 ± .14	43.41 ± 7.75
10% in Vehicle A	7.5	1.084 ± .11	2.364 ± .22	53.32 ± 4.17
15% in Vehicle A	7.5	0.768 ± .10	2.443 ± .15	68.77 ± 3.02
20% in Vehicle A	8.0	0.307 ± .08	1.844 ± .28	83.78 ± 3.66
20% in Vehicle B	7.0	0.261 ± .01	1.653 ± .15	83.37 ± 1.46
10% in Vehicle F	5.5	0.679 ± .08	1.436 ± .20	49.89 ± 5.54
20% in Vehicle F	5.5	0.324 ± .08	1.491 ± .14	78.43 ± 4.39

It will be appreciated by those skilled in the art that the invention can be performed within a wide range of equivalent parameters of composition and conditions without departing from the spirit or scope of the invention or of any embodiment thereof.

C L A I M S

1. A process of inhibiting mammalian hair growth, comprising applying to the skin a composition including an inhibitor of cyclooxygenase in an amount effective to reduce hair growth.

2. The process of claim 1, wherein said inhibitor is one or more of α-methyl-4-[2-methylpropyl]benzeneacetic acid, 6-methoxy-α-methyl-2-naphthaleneacetic acid, 2-[3-phenoxyphenyl]propionic acid, 2-[3-benzoylphenyl]propionic acid, gamma-oxo-[1,1'-biphenyl]-4-butanoic acid, 6-chloro-α-methylcarbazole-2-acetic acid, 1-[p-chlorobenzoyl]-5-methoxy-2-methylindole-3-acetic acid, 5-fluoro-2-methyl-1-[(4-(methylsulfinyl)phenyl)methylene]-1H-indene-3-acetic acid, 1-methyl-5-[p-toluoyl]pyrrole-2-acetic acid, 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid, 2-acetoxybenzoic acid, 5-[2,4-difluorophenyl]salicylic acid, 2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid, 2-[(2,3-dimethylphenyl)amino]benzoic acid, 4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide, or 4-[6-methoxy-2-naphthyl]-2-butanone.

3. The process of claim 1, wherein said inhibitor is a nonsteroidal anti-inflammatory drug.

4. The process of claim 3, wherein said nonsteroidal anti-inflammatory drug is one or more of a propionic acid, an indolacetic acid, a salicylate, an anthranilic acid, or an enolic acid.

5. The process of claim 1, wherein the concentration of said inhibitor in said composition is between 1% and 30%.

6. The process of claim 1, wherein the composition is applied to the skin in an amount of from 100 to 3000 micrograms of said inhibitor per square centimeter of skin.

7. The process of claim 1, wherein the composition is applied to the skin on the face of said mammal.

8. A method of producing a composition for inhibiting mammalian hair growth, which comprises selecting an inhibitor of cyclooxygenase, and combining said inhibitor, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle or carrier.

9. A method according to claim 8, wherein said vehicle or carrier is adapted to be spread upon the skin of a mammal.

10. A method according to claim 8, wherein said inhibitor is as defined in any one of claims 2 to 5.

11. The new use of an inhibitor of cyclooxygenase for reducing hair growth.

12. A composition when used for inhibiting hair growth, which includes an inhibitor of cyclooxygenase in an amount effective to reduce hair growth and a non-toxic, dermatologically acceptable vehicle or carrier.

13. A composition according to claim 12, wherein said inhibitor is as defined in any one of claims 2 to 5.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/12 A61K31/19 A61K31/40 A61K31/405 A61K31/54
A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 321 952 (L'OREAL) 28 June 1989 ---	
A	J. PHARM. SOC. JPN, vol.113, no.10, 1993 pages 718 - 724 N. KOBAYASHI ET AL. 'Effects of Ginko biloba on hair regrowth in C3h strain mice.' -----	

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INTERNATIONAL SEARCH REPORT

information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0321952	28-06-89	LU-A-	87090	07-07-89
		DE-A-	3873895	24-09-92
		JP-A-	1211523	24-08-89
		US-A-	5053410	01-10-91